NTP Toxicological Study Nomination Procedures

Nominations to the Testing Program http://ntp.niehs.nih.gov/go/nom

The NTP maintains a balanced research and testing program that provides data addressing a wide variety of issues important to public health. The NTP actively seeks to identify and select for study chemicals and other substances for which sufficient information is not available to adequately evaluate potential human health hazards. The NTP accomplishes this goal through a formal open nomination and selection process. Substances considered appropriate for study generally fall into two broad yet overlapping categories:

1. Substances judged to have high concern as a possible public health hazard based on the extent of human exposure and/or suspicion of toxicity.
2. Substances for which toxicological data gaps exist and additional studies would aid in assessing potential human health risks, e.g. by facilitating cross-species extrapolation or evaluating dose-response relationships.

Input is also solicited regarding the nomination of studies that permit the testing of hypotheses to enhance the predictive ability of future NTP studies, address mechanisms of toxicity, or fill significant gaps in the knowledge of the toxicity of classes of chemical, biological, or physical substances. Increased efforts continue to be focused on:

1. Improving the quality of the nominations of chemicals, environmental agents, or issues for study so that public health and regulatory needs are addressed.
2. Broadening the base and diversity of nominating organizations and individuals.
3. Increasing nominations for studying toxicological endpoints in addition to carcinogenesis.

How to Nominate a Substance or Issue for Study http://ntp.niehs.nih.gov/go/602

The nomination and selection for study of chemicals and other substances with the highest potential for adversely impacting public health are essential to the success of the Program. From its inception, the NTP has had an open nomination process. Nominations are solicited from sources in academia, Federal and State regulatory and health agencies, industry, and unions, as well as from advocacy groups and the general public. Particular assistance is sought with the selection of studies that address issues such as testing of hypotheses to enhance the predictive ability of NTP studies, mechanisms of toxicity, or filling significant gaps in knowledge of the toxicity of chemicals or classes of chemicals.

Substances are studied for a variety of health-related effects, including but not limited to, reproductive and developmental toxicity, genotoxicity, immunotoxicity, metabolism and disposition, and carcinogenicity. The possible public health consequences of exposure remain the over-riding factor in the decision to study a particular substance. Selections for government testing are based on the principle that responsible industries will evaluate their own products for

health and environmental effects as mandated by Congress under legislative authorities. Nominations to the NTP should be based on one or more of the principles listed below.

Nomination Principles for NTP Studies

The NTP is an interagency program whose mission is to evaluate chemical, biological, and physical agents (collectively referred to as "substances") of public health concern by developing and applying tools of modern toxicology and molecular biology. The NTP operates under the general principle that industry will evaluate substances for health and environmental effects as intended and mandated by Congress under legislative authorities. Therefore the NTP, acting to carry out its mission, solicits nominations for NTP studies from the following categories:

1. Substances found in home, workplace, or ambient environments that are not associated with a single commercial organization.
2. Naturally occurring substances that may not be adequately evaluated without federal involvement.
3. Commercial products with significant exposure that were first marketed prior to current testing requirements or those that generate too little revenue to support further evaluations.
4. Potential substitutes for existing chemicals or drugs that might not be developed without federal involvement.
5. Mixtures of substances for which evaluations are not required of industry.
6. Substances that will aid our understanding of chemical toxicities, or our understanding of the use of test systems to evaluate potential toxicities.
7. Substances that should be evaluated to improve the scientific understanding of structure-activity relationships and thereby help limit the number of substances requiring extensive evaluations.
8. Emergencies or other events that warrant immediate federal government evaluation of a substance.

Prior to committing to specific studies, the NTP assesses the needs for studies by: evaluating existing literature and testing data, assessing ongoing evaluations in the government and private sector, and determining how the nomination fits into an overall plan for improving current test methods. The selection of a substance or issue for study by the NTP does not automatically commit the NTP to its evaluation. The NTP considers priorities for nominated studies at many phases: when the nomination is reviewed and evaluated for possible study, when the study is being designed, and again when the NTP considers the most appropriate intramural or extramural mechanism to conduct the study. The NTP may defer a study during any of these phases if suitable data become available, if higher priority studies are identified, or if the study proves to be impractical.

Nominations should be addressed to:

Office of Chemical Nomination and Selection, National Toxicology Program/NIEHS, MD A3-07, P.O. Box 12233, Research Triangle Park , NC, 27709

NTP Nomination Sources

Member agencies of the National Toxicology Program (FDA, NIEHS, and NIOSH) and other sources (including other Federal agencies, state agencies, the public, labor, and industry) submit nominations of substances and issues to the NTP for toxicological testing.

All nominating sources are asked to identify when possible: the particular toxicological information needed; the rationale for the nomination; any available background data on production, use, exposure, environmental occurrence; and the extent of available toxicological information (See Nomination Elements below). However, it is recognized that all potential nomination sources do not have the resources to obtain all the requested information. Therefore, all nominations are considered regardless of the extent of the information submitted.

Nomination Elements

i. Chemical Identification
   a. Chemical Abstracts Service (CAS) preferred name
   b. Common or generic name and synonyms
   c. CAS Registry Number
   d. Chemical class and related compounds
   e. Physical and chemical properties
      i. Physical description
      ii. Structural and molecular formula and molecular weight
      iii. Melting and boiling points
      iv. Solubility
      v. Stability and reactivity
      vi. Other relevant information
   f. Commercial product(s) composition

ii. Production, Use, Occurrence, and Analysis
   a. Production
      i. Source and synthesis
      ii. Current production and pathway
   b. Uses
   c. Occurrence in the Environment
      i. Naturally occurring
      ii. Air, water, and soil
   d. Analysis

iii. Toxicology
   a. Human data, case reports, and epidemiological studies
   b. Experimental animal studies
   c. *In vitro* and other short-term tests
   d. Other relevant information

iv. Disposition and Structure-activity relationships
   a. Absorption, distribution, metabolism and excretion

b. Structure-activity correlations and considerations
v. Ongoing Toxicological Studies in the Government, Industry, and Academe
vi. Rationale for Recommendation and Suggested Studies
vii. References

Study Nomination Review & Selection Process
http://ntp.niehs.nih.gov/go/603

The review and selection of substances and issues nominated for study is a multi-step process. A broad range of concerns are addressed during this process through the participation of representatives from the NIEHS, other Federal agencies, the NTP Board of Scientific Counselors, the NTP Executive Committee, and the public. This multi-step evaluative process provides the NTP with direction and guidance to ensure that its testing program addresses toxicological concerns relative to all areas of public health, and furthermore, that there is balance among the types of substances selected for study (e.g., industrial chemicals, consumer products, therapeutic agents). As such, it should be recognized that at any given time, the new study nominations under consideration do not necessarily reflect the overall balance of substances historically or currently being evaluated by the NTP in its toxicology testing program.

Receipt and Initial Review

Nominations are reviewed by the NTP Office of Chemical Nomination and Selection to determine whether they have been adequately tested or have been previously considered by the NTP. For nominations not eliminated from consideration or deferred at this stage, the available literature is examined in detail to prepare a Review of Toxicological Literature which evaluates and summarizes the relevant data for each chemical. The Review of Toxicological Literature serves as the supporting document of record for the nomination and addresses the types of information found in the NTP Study Nomination Elements. In some cases, supporting documents are prepared by the nominator and submitted along with the nomination.

Interagency Committee for Chemical Evaluation and Coordination (ICCEC) Review

The nomination supporting documents along with relevant supporting information supplied by the nominator as appropriate are distributed to the Interagency Committee for Chemical Evaluation and Coordination (ICCEC). The ICCEC is composed of representatives from the Agency for Toxic Substances and Disease Registry/ National Center for Environmental Health, U.S. Consumer Product Safety Commission, U.S. Department of Defense, U.S. Environmental Protection Agency, U.S. Food and Drug Administration's National Center for Toxicological Research, National Institutes of Health's (NIH) National Cancer Institute, NIH's National Institute of Environmental Health Sciences (NIEHS), National Institute for Occupational Safety and Health, NIH's National Library of Medicine, and the Occupational Safety and Health Administration. The ICCEC meets once or twice annually to evaluate groups of new study

nominations and to make recommendations with respect to both specific types of studies and testing priorities.

Public Comment

A Federal Register notice listing the nominations reviewed by the ICCEC and the recommended studies is published. The Federal Register notice marks the beginning of a formal public comment period and solicits comments on the nominations and study recommendations from interested parties including information on completed, ongoing, or planned testing in other government organizations and the private sector.

NTP Board of Scientific Counselors & NTP Executive Committee Review

Supporting documents, the ICCEC's study recommendations, and any public comments received on the nominations are then presented to the NTP Board of Scientific Counselors for review and comment in a public meeting. This public meeting also provides and opportunity for the NTP to receive additional public comments. The Board provides independent advice to the NTP on the study recommendations for each nomination, and may suggest additional studies as well as their perspective on study priority and issues raised by public comments.

All information on each nomination gathered to this point is then provided to the NTP Executive Committee. The Executive Committee reviews each nomination and makes a final recommendation to the NTP Director on whether to test, defer, or not test each of the nominated substances for the various types of study.

Implementation of Study Recommendations

Each nomination selected for study is assigned to an NIEHS, FDA, or NIOSH staff scientist (project leader) who assesses the data compiled during the nomination review and selection process and other pertinent current information.

Project leaders together with a Study Design Team develop a study plan to address the research needs, or may recommend not pursuing study. Such a recommendation may be based upon technical difficulties in studying the chemical, its lack of availability, or the existence of adequate outside testing. If a study is warranted, the project leader, with approval of the Study Design Team, presents a study proposal to an NIEHS/NTP project review committee. All substances and issues selected as a result of this process are then studied as time and resources permit.